Sir:

In response to the Office Action dated October 10, 2002, please amend the above-identified application as follows and consider the following remarks. This response is accompanied by an Amendment Transmittal, a computer readable form (diskette) of the Sequence Listing, a paper copy of the Sequence Listing, and a Petition for Extension of Time, up to and including January 10, 2003. Please note that the October 10, 2002 Action was not accompanied by a Notice to Comply.

It is believed that no other fees except for payment for two months extension of time are required for these submissions. However, should the United States Patent and Trademark Office determine that any other fee is due or that any refund is owed for this application, the Commissioner is hereby authorized and requested to charge the required fee(s) and/or credit the refund(s) owed to our Deposit Account No. 04-0100.

IN THE CLAIMS:

Please cancel claims 28-54. Please add the following new claims:

55. (New) A transgenic non-human mammal whose genome comprises:

(a) a nucleotide sequence encoding a human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the regulatable promoter in the absence of a repressor-activator fusion polypeptide-binding compound and does not bind to the regulatable promoter in the presence of the compound, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a chondrocyte tissue-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the mammal until adulthood, and wherein the metalloproteinase is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mammal.

56. (New) The transgenic mammal of claim 55, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

57. (New) The transgenic mammal of claim 56, wherein the matrix metalloproteinase is MMP-13.

58. (New) The transgenic mammal of claim 57, wherein the MMP-13 is constitutively active.

59. (New) The transgenic mammal of claim 58, wherein the MMP-13 comprises the sequence of SEQ ID NO:1 or SEQ ID NO:21.

60. (New) The transgenic mammal of claim 55, wherein the repressor-activator fusion polypeptide is a chimeric tetracycline repressor-VP16 transcription activator polypeptide and the regulatable promoter is a Tn10 sèquence linked to a portion of the CMV IE promoter.

61. (New) The transgenic mammal of claim 60, wherein the regulatable promoter comprises the sequence of SEQ ID NO:2.

62. (New) The transgenic mammal of claim 55, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of Type II collagen into a TC^A

degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

63. (New) The transgenic mammal of claim 55, wherein the chondrocyte tissue-specific promoter is a Type II collagen promoter.

64. (New) A transgenic rat whose genome comprises:

(a) a nucleotide sequence encoding a human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a tetracycline-regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the tetracycline regulatable promoter in the absence of tetracycline or a tetracycline analog and does not bind to the regulatable promoter in the presence of tetracycline or tetracycline analog, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a chondrocyte tissue-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the rat until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the rat.

65. (New) The transgenic rat of claim 64, wherein the matrix metalloproteinase is constitutively enzymatically active MMP-13, the tetracycline-regulatable promoter is tet07, the repressor-activator fusion polypeptide is tTA, and the chondrocyte tissue-specific promoter is a Type II collagen promoter.

66. (New) The transgenic rat of claim 64, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

67. (New) A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 55 in presence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by withholding the compound from the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic mammal.

68. (New) The method according to claim 67, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

69. (New) A method for producing degradation of Type II collagen in the joints of a transgenic mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 60 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the mammal after the mammal has reached

adulthood, such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic mammal.

70. (New) The method according to claim 69, wherein the tetracycline analog is doxycycline.

71. (New) The method according to claim 69, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

72. (New) A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises

(a) maintaining the transgenic rat of claim 64 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the rat after the rat has reached adulthood, such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic rat.

73. (New) The method according to claim 72, wherein the tetracycline analog is doxycycline.

74. (New) The method according to claim 72, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte

formation, or combinations thereof.

75. (New) A transgenic non-human mammal whose genome comprises:

(a) a nucleotide sequence encoding a human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a transcription activator protein that binds to the regulatable promoter in the presence of a transcription activator protein-binding compound and does not bind to the regulatable promoter in the absence of the compound, which nucleotide sequence encoding the transcription activator protein is operatively linked to a chondrocyte tissue-specific promoter;

wherein expression of the metalloproteinase is capable of being repressed in the mammal until adulthood, and wherein the metalloproteinase is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mammal.

76. (New) The transgenic mammal of claim 75, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

77. (New) The transgenic mammal of claim 76, wherein the matrix metalloproteinase is MMP-13.

78. (New) The transgenic mammal of claim 77, wherein the MMP-13 is constitutively active.

79. (New) The transgenic mammal of claim 78, wherein the MMP-13 comprises the sequence of SEQ ID NO:1 or SEQ ID NO:21.

80. (New) The transgenic mammal of claim 75, wherein the chondrocyte tissue-specific promoter is a Type II collagen promoter.

81. (New) The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to an ecdysone receptor ligand-binding domain, and wherein the transgenic mammal further comprises a nucleotide sequence encoding a retinoid X receptor (RXR), which nucleotide sequence encoding RXR is operatively linked to a chondrocyte tissue-specific promoter.

82. (New) The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a progesterone receptor ligand-binding domain.

83. (New) The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a steroid binding domain.

84. (New) The transgenic mammal of claim 75, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

85. (New) A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 75 in the absence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering the compound to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

86. (New) A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 81 in the absence of ecdysone, an ecdysone analog, or dexamethasone until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering ecdysone, an ecdysone analog, or dexamethasone to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

87. (New) A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 82 in the absence of mifeprestone (RU 486) until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering mifepristone (RU 486) to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

88. (New) The method according to claim 86, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte

formation, or combinations thereof.

89. (New) The method according to claim 87, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

90. (New) A method for evaluating potential of a compound to counteract degradation of Type II collagen in joints of a non-human mammal, which method comprises:

(a) administering the compound to the transgenic mammal of claim 55 in which expression of the metalloproteinase has been activated during adulthood; and

(b) comparing the extent of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation in the mammal to which the compound was administered relative to a control mammal in which expression of the metalloproteinase was activated without administering the compound,

wherein any less extensive development in the nature or extent of, or any increased length of time required for the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation to develop in the mammal that has been

administered the compound relative to the control mammal, indicates the potential of the compound to counteract degradation of Type II collagen in joints of a mammal.

91. (New) A method for evaluating potential of a compound to counteract degradation of Type II collagen in joints of a mammal, which method comprises:

(a) administering the compound to the transgenic mammal of claim 60 in which expression of the metalloproteinase has been activated during adulthood; and

(b) comparing the extent of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation in the mammal to which the compound was administered relative to a control mammal in which expression of the metalloproteinase was activated without administering the compound,

wherein any less extensive development in the nature or extent of, or any increased length of time required for the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation to develop in the mammal that has been administered the compound relative to the control mammal, indicates the potential of the compound to counteract degradation of Type II collagen in joints of a mammal.

92. (New) A method for evaluating potential of a compound to counteract degradation of Type II collagen in joints of a mouse or rat, which method

comprises:

(a) administering the compound to the transgenic mouse or rat of claim 64 in which expression of the metalloproteinase has been activated during adulthood; and

(b) comparing the extent of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation in the mouse or rat to which the compound was administered relative to a control mouse or rat in which expression of the metalloproteinase was activated without administering the compound,

wherein any less extensive development in the nature or extent of, or any increased length of time required for the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation to develop in the mouse or rat that has been administered the compound relative to the control mouse or rat, indicates the potential of the compound to counteract degradation of Type II collagen in joints of a mouse or rat.

93. (New) A method for evaluating potential of a compound to counteract degradation of Type II collagen in joints of a mammal, which method comprises:

(a) administering the compound to the transgenic mammal of claim 75 in which expression of the metalloproteinase has been activated during adulthood; and

(b) comparing the extent of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation in the mammal to which the compound was administered relative to a control mammal in which expression of the metalloproteinase was activated without administering the compound,

wherein any less extensive development in the nature or extent of, or any increased length of time required for the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation to develop in the mammal that has been administered the compound relative to the control mammal, indicates the potential of the compound to counteract degradation of Type II collagen in joints of a mammal.

94. (New) A method for evaluating potential of a compound to counteract degradation of Type II collagen in joints of a mammal, which method comprises:

(a) administering the compound to the transgenic mammal of claim 81 in which expression of the metalloproteinase has been activated during adulthood; and

(b) comparing the extent of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation in the mammal to which the compound was administered

relative to a control mammal in which expression of the metalloproteinase was activated without administering the compound, wherein any less extensive development in the nature or extent of, or any increased length of time required for the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation to develop in the mammal that has been administered the compound relative to the control mammal, indicates the potential of the compound to counteract degradation of Type II collagen in joints of a mammal.

95. (New) A method for evaluating potential of a compound to counteract degradation of Type II collagen in joints of a mammal, which method comprises:

(a) administering the compound to the transgenic mammal of claim 82 in which expression of the metalloproteinase has been activated during adulthood; and

(b) comparing the extent of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation in the mammal to which the compound was administered relative to a control mammal in which expression of the metalloproteinase was activated without administering the compound, wherein any less extensive development in the nature or extent of, or any increased length of time required for the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing,

destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation to develop in the mammal that has been administered the compound relative to the control mammal, indicates the potential of the compound to counteract degradation of Type II collagen in joints of a mammal.

96. (New) A method for evaluating potential of a compound to counteract degradation of Type II collagen in joints of a mammal, which method comprises:

(a) administering the compound to the transgenic mammal of claim 83 in which expression of the metalloproteinase has been activated during adulthood; and

(b) comparing the extent of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation in the mammal to which the compound was administered relative to a control mammal in which expression of the metalloproteinase was activated without administering the compound,

wherein any less extensive development in the nature or extent of, or any increased length of time required for the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation to develop in the mammal that has been administered the compound relative to the control mammal, indicates the potential of the compound to counteract degradation of Type II collagen in joints of a mammal.